Development of Olaparib for BRCA-Deficient Recurrent Epithelial Ovarian Cancer

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Disclosure of Potential Conflicts of Interest

R.N. Eskander reports receiving speakers bureau honoraria from AstraZeneca. B.J. Monk reports receiving speakers bureau honoraria from AstraZeneca, and is a consultant/advisory board member for AstraZeneca and TESARO. No potential conflicts of interest were disclosed by the other author.
Abstract

The FDA approval of the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, for fourth-line therapy of germline BRCA 1/2 mutated ovarian cancer represents the first registered indication for this class of drugs in any disease. PARP is a family of proteins involved in the repair of single-strand DNA breaks. High-grade serous ovarian carcinomas with BRCA deficiencies may be particularly vulnerable to both direct and indirect effects of PARP inhibition. This phenotype frequently arises as a consequence of defects in the repair of damaged DNA, rendering cancer cells susceptible to DNA-damaging platinum compounds and targeted therapies impacting homologous recombination repair (HRR). When cells already deficient in HRR are exposed to PARP inhibitors, apoptosis occurs by way of synthetic lethality.

In this review, we trace the clinical development of olaparib for women with recurrent epithelial ovarian carcinoma harboring germline BRCA mutations, a biomarker for HRR deficiency present in 15-20% of cases. Clinical trials highlighted include not only those pivotal studies which have led to regulatory approval in the United States and in Europe, but also those in which olaparib was studied in novel combinations, including chemotherapy and anti-angiogenesis agents.
Introduction

Ovarian cancer is the most lethal gynecologic cancer with 21,290 new cases and 14,180 deaths anticipated for 2015 in the United States (US) (1). The lack of validated screening tools in the general population together with an absence of specific symptoms indicative of early disease accounts for the poor 5-year survival (1). The most common histologic subtype of epithelial ovarian (and fallopian tube) cancer is high-grade serous and is characterized by genetic instability and almost universal p53 dysfunction (1).

Synthetic lethality occurs when a genetic defect or defective protein is compatible with cell viability but is lethal when combined (i.e., synthesized) with another genetic/protein defect (1,2). The most robust demonstration of the principle of harnessing synthetic lethality comes from the treatment of cancers resulting from loss of BRCA gene function. The discovery of BRCA1 and BRCA2 (BRCA1/2) are among the most important discoveries in human cancer genetics. The BRCA genes encode proteins involved in error-free repair of DNA double-strand breaks.

Poly (ADP-ribose) polymerase (PARP) 1 is necessary for repair of DNA single-strand breaks (Fig. 1). PARP1 binds DNA and synthesizes PARP chains through PARylation (1,2). Post-translational modification of substrate proteins leads to recruitment of DNA repair effectors such as XRCC1 to the site of the single-strand break. PARP1 is released from the damaged DNA through auto-PARylation (1,2).

Early Phase I and Phase II Monotherapy Trials
Clinical trials of interest appear in Tables 1 (3-15) and 2 (phase II and randomized phase II) (16-24). In the initial accelerated dose-escalation phase I study, Fong et al reported the maximal tolerated dose (MTD) of the oral PARPi olaparib was 400 mg two times a day (BID) (Table 1) (3). Toxicities (myelosuppression and central nervous system effects) were mild and self-limited. Included in the 60-patient study were 19 BRCA1/2-deficient patients with breast, ovarian, or prostate cancer, for whom the observed objective response rate (ORR) was 47% and the disease control rate (DCR) was 63% (3). A secondary analysis involving a planned expansion of this study enriched with BRCA mutated cases only suggested that the most favorable responses to olaparib were among platinum-sensitive patients (ORR 69%) as compared to those who were platinum-resistant (ORR 23%) (4). The relationship between prior platinum response and PARPi sensitivity is explored further below and may result from the ability of both PARP inhibitors and platinum salts to stall replication forks and cause DNA damage that otherwise would be repaired through BRCA-mediated homologous recombination in the wildtype setting (2).

Phase II trials in both refractory breast and ovarian cancer studied olaparib at both the previously identified MTD dose of 400 mg BID, and a lower dose of 100 mg BID (16, 17) (Table 2). Audeh et al reported the phase II study in women with BRCA-deficient ovarian cancer, for whom the median number of prior regimens was three (17). Two sequential cohorts were enrolled comprising 33 patients treated with the MTD, followed by 24 who received the lower dose. The higher dose was associated with a higher ORR (33% vs 13%) and two cases (6%) of grade 3-4
nausea, one case (3%) of grade 3-4 fatigue, and one case (3%) of grade 3-4 anemia (17). These early studies served as a proof-of-concept for the clinical application of synthetic lethality.

Later Phase II and Randomized Phase II Trials of Monotherapy and Maintenance Therapy

Because of the molecular, histopathological, and clinical similarities (ie., BRCAAness) shared between both high-grade serous ovarian cancer and triple negative breast and germline BRCA-deficient cancers, these two subtypes were selected for further study with PARP inhibition (Table 2). Gelmon et al performed a phase II, non-randomized study of olaparib (400 mg BID) in BRCA-positive and -negative patients with advanced high-grade serous and/or undifferentiated ovarian cancer (n=65) and triple-negative breast cancer (n=26) (18). Among those with ovarian cancer, confirmed objective responses were seen in seven (41%; 95% CI 22-64) of 17 patients with BRCA1/2 mutations and 11 (24%; 95% CI 14-38) of 46 without mutations (18). Responses correlated with prior platinum sensitivity. No confirmed objective responses were observed in the breast cancer cohort, although tumor-reduction effects and disease-stabilization was higher in the mutants. Fatigue and nausea occurred in 50% or greater in both subpopulations (18).

Kaufman et al studied olaparib (400 mg BID) in a spectrum of BRCA1/2-mutated cancers in Study 42 (19). Enrollment was restricted to germline BRCA1/2-positive patients with 1) platinum resistant recurrent ovarian cancer, 2) metastatic breast cancer following three or more chemotherapy regimens, 3) pancreatic cancer with prior gemcitabine treatment, or 4) prostate cancer with progression on
hormonal therapy and one systemic therapy. In the entire cohort of 298 evaluable patients, the ORR was 26.2% overall (19). The highest responses were reported in patients with prostate (50.0%, n=4 of 8) and ovarian cancer (31.1%, n=60 of 193; 95% CI 24.6-38.1) (19). Only 8 (12.9%; 95% CI 5.7-23.9) of the 62 women with breast cancer experienced objective tumor response by RECIST criteria. Grade 3 or higher adverse events (AEs) were reported for 54% of patients with anemia (17%) being most common (19).

The first randomized phase II study of olaparib was reported by Kaye et al and included nearly 100 women with BRCA1/2-positive, recurrent ovarian cancer who were randomized to two different dosages of olaparib or to two different dosages of pegylated liposomal doxorubicin (PLD) (Table 2) (20). Equivalence of all three arms for progression free-survival (PFS) and ORR was reported, with the activity and tolerability of olaparib consistent with previous studies.

Ledermann et al performed a randomized, double-blind, placebo-controlled, phase II study using olaparib as maintenance therapy (400 mg BID) among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen (21). This trial is known as Study 19 and it’s primary endpoint, PFS, was significantly longer with olaparib than with placebo (median 8.4 vs 4.8 mos; hazard ratio (HR) for progression or death, 0.35; 95% CI, 0.25-0.49; p<0.001) (Table 2) (21). The majority of AEs were grade 1-2 and those occurring by more than 10% in the olaparib group compared with placebo included, nausea, fatigue, vomiting, and anemia.
Of those patients in the trial with known BRCA status, 74 (56%) in the olaparib group and 62 (50%) in the placebo group had a deleterious or suspected germline BRCA mutation (22). In a protocol-specified retrospective analysis stratified by mutational status, Ledermann et al reported that among BRCA-deficient cancers, those treated with olaparib had a significantly longer median PFS as compared to the placebo group (11.2 vs 4.3 mos; HR 0.18; p<0.0001) (22). Thus far, two interim analyses suggest that overall survival (OS) is not significantly different between the olaparib and placebo cohorts, whether stratified by mutation status or not.

**Olaparib in Combination with Chemotherapy**

Clinical development of olaparib has included multiple attempts to combine the PARP inhibitor with chemotherapy. In the phase I trial reported by Samol et al (Table 1) (7), the combination of olaparib plus topotecan was associated with significant dose-limiting hematologic AEs resulting in a subtherapeutic MTD, essentially halting further development of this combination. The combination of olaparib with cisplatin plus gemcitabine was piloted by Rajan et al who reported significant myelosuppression even at relatively low dosages (Table 1) (8). Similarly, a MTD could not be determined for the combination of olaparib plus weekly paclitaxel which was complicated by significant clinical interaction and greater than expected rates of neutropenia despite secondary prophylaxis (9). In phase I studies evaluating continuous and intermittent dosing of olaparib with cisplatin (11) or with gemcitabine (12), only chemotherapy combined with intermittent dosing of olaparib at 50 mg (days 1-5) or 100 mg (days 1-14).
At the recent 2015 Annual Meeting of the American Society of Clinical Oncology, Chiou et al reported results from their Phase I/Ib trial of olaparib with escalating dosages of carboplatin in heavily pre-treated patients with high-grade serous ovarian cancer with low genetic risk (13). The median number of prior therapies was six. Among evaluable subjects, platinum-sensitive patients (n=11) experienced a higher ORR than those with platinum-resistant disease (n=14) (36% vs 7%).

In an open-label, phase II study (Study 41), Oza et al randomized 162 women with platinum-sensitive high-grade serous ovarian cancer who had remained progression-free for a minimum of 6 months prior to study entry to carboplatin (AUC 4) plus paclitaxel (175 mg/m²) with and without olaparib 200 mg BID d1-10, followed by 400 mg BID monotherapy continuously (23). The arm administering olaparib was associated with significantly improved PFS (Table 2), with the greatest benefit conferred to those with known BRCA mutations (n=20; HR 0.21; 95% CI 0.08-0.55; p=00015) (23). Serious AEs were reported in 15% of patients in the olaparib plus chemotherapy arm as compared with 21% in the chemotherapy alone group. Interestingly, when comparing the hazard of progression for the platinum-sensitive BRCA-mutated patients in this study (23) to that of the platinum-sensitive BRCA-mutation positive patients in Study 19 (21) (HR 0.21 vs 0.18, respectively), it would appear that there is no additional benefit to adding olaparib to chemotherapy.

**Olaparib in Combination with Anti-angiogenic Agents**
Phase I studies of olaparib (400 mg BID) combined with drugs that target the vascular endothelial growth factor (VEGF) axis have been informative, with no dose limiting toxicities (DLTs) reported in the olaparib plus bevacizumab trial (Table 1) (14). Provocative data from the phase I combining olaparib with cediranib identified the MTD (Table 1) (15) and led directly to a randomized phase II study of 46 women with either measureable platinum-sensitive, recurrent, high-grade serous, or endometrioid ovarian carcinoma or those with deleterious germline \textit{BRCA1/2} mutations (Table 2) (24). Compared to olaparib monotherapy, the combination was associated with significantly improved PFS (17.7 vs 9.0 mos; HR 0.42; 95% CI 0.23-0.76; \(p=0.005\)) (24). Grade 3 and 4 fatigue, diarrhea, and hypertension were more common with combination therapy (24). The olaparib plus cediranib combination may constitute a chemotherapy-free alternative for select patients with recurrent disease.

\section*{Regulatory Approval of Olaparib in the United States}

During February 2014, AstraZeneca filed a US regulatory submission for olaparib as a maintenance therapy in platinum-sensitive recurrent disease based on Study 19 (21). On June 25, 2014, the Oncology Drugs Advisory Committee (ODAC) panel members voted 11 to 2 against regulatory approval of olaparib and in response to a request by the FDA for additional data, AstraZeneca submitted a major amendment to their New Drug Application on July 24, 2014, highlighting Study 42 (19).

These data prompted the FDA to extend the original October 3, 2014 Prescription Drug User Fee Act action date to January 3, 2015. On December 19,
2014, the FDA granted accelerated approval to olaparib as fourth-line therapy for women with BRCA-deficient (germline only) ovarian carcinoma. Approval was based on the analysis of 137 patients from Study 42 with measureable BRCA-deficient recurrent disease treated with three or more prior lines of chemotherapy. The ORR for this cohort was 34% (95% CI, 26%-42%) and the median duration of response was 7.9 mos (95% CI, 5.6-9.6 mos).

The ongoing phase III randomized study, SOLO 2 (NCT01874353), and its successor SOLO 3 (02282020), are integral to the phase VI commitment following accelerated approval. FDA approval was done in conjunction with regulatory approval of a companion diagnostic genetic test (BRCAnalysis CDx) that will screen serum from ovarian cancer patients for mutations in the BRCA genes (gBRCAm). Interestingly, one day before regulatory approval in the US, AstraZeneca announced on December 18, 2014 that the European Commission granted marketing authorization for olaparib as a first-line maintenance therapy of adult patients with platinum-sensitive, relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, tubal, or peritoneal carcinoma.

The clinical implications of approving a drug for fourth-line therapy need to be framed in the context of toxicity assessment. This is particularly important in the setting of recurrent disease where quality of life/disease control, is the goal and not cure. Contemporary regimens for recurrent platinum sensitive disease include carboplatin (or cisplatin) plus either paclitaxel or gemcitabine, and carboplatin plus PLD. Women with partially platinum sensitive and platinum resistant disease may receive bevacizumab plus either PLD, topotecan, or weekly paclitaxel or
monotherapy using PLD, topotecan, weekly albumin-stabalized nanoparticle formulation paclitaxel, trabectedin, or pemetrexed (the latter two not having a label in the US). Olaparib as monotherapy may have a much more favorable safety profile compared to conventional chemotherapy used in the recurrent setting.

Discussion

All patients will ultimately progress on olaparib. Based on pre-clinical data, early essayists were concerned that treatment with PARP inhibitors would result in acquisition of secondary BRCA1/2 mutations that would limit the efficacy of subsequent chemotherapy, specifically, platinum-based agents. Ang et al collected data from 89 patients with BRCA-deficient ovarian cancer who had been previously treated with olaparib at daily dosages of 200 mg and higher (25). The ORR by RECIST to post-olaparib chemotherapy was 36% (n=24 of 67 patients). For patients treated post-olaparib with platinum-based chemotherapy the ORR was 40% (n=19 of 48 patients (25). The corresponding ORRs when incorporating CA-125 were 45% and 49%, respectively (925). The length of the platinum-to-platinum interval with intervening olaparib was associated with an increased likelihood of response (25). Tumor was available from six cases and subjected to massively parallel sequencing which demonstrated no evidence of secondary BRCA mutations (25). These data suggest that not only does PARP inhibitor-resistant ovarian cancer retain the potential to respond to chemotherapy, but that treatment with PARP inhibitors may enhance the response to subsequent platinum.

Using targeted capture and massively parallel genomic sequencing, Pennington et al recently reported that germline (24%) and somatic (9%)
mutations were detected in one or more of 13 homologous recombination genes, including \textit{BRCA1}, \textit{BRCA2}, \textit{ATM}, \textit{BARD1}, \textit{BRIP1}, \textit{CHEK1}, \textit{CHEK2}, \textit{FAM175A}, \textit{MRE11A}, \textit{NBN}, \textit{PALB2}, \textit{RAD51C}, and \textit{RAD51D} (26). Homologous recombination deficiency was found in both serous and non-serous ovarian carcinomas including clear cell, endometrioid, and ovarian carcinosarcoma. Both germline and somatic homologous recombination mutations were highly predictive of platinum sensitivity and improved OS, with OS rates of 66 months (germline), 59 months (somatic), and 41 months (no homologous recombination deficiency) noted (26). These data support interrogating ovarian tumors for genomic scars indicative of homologous recombination deficiency to assess candidacy for treatment with olaparib and other PARP inhibitors.

\section*{Conclusion}

Moving forward, the prevalence of homologous recombination deficiency in tumors other than ovarian and breast require assessment and predictive biomarkers need to be discovered. In addition, indications for combining olaparib with chemotherapy and additional chemotherapy-free olaparib-based regimens should be explored.

Regulatory approval of the first-in-class PARP inhibitor, olaparib, as a monotherapy for patients with BRCA-deficient or suspected BRCA-deficient recurrent ovarian cancer is accompanied by discrete consequences for drug development in the fourth-line space. At the very minimum, newer agents will have to deliver ORR in excess of 30\% with the lower limit of a 95\% confidence interval settling in at 26-28\%.
Acknowledgments

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References


24. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with


Table 1. Selected phase I studies of olaparib

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>DOSE &amp; SCHEDULE</th>
<th>DLT</th>
<th>MTD</th>
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<tbody>
<tr>
<td><strong>OLAPARIB MONOTHERAPY</strong></td>
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<tr>
<td>Fong PC, et al (3)</td>
<td>Advanced solid tumors, selection aimed to enrich BRCA 1/2 mutation carriers</td>
<td>Olaparib 10 mg qd PO x 2 wks q21d up to 600 mg BID PO qd</td>
<td>G3 mood alteration and fatigue (n=1; 400 mg BID); G4 thrombocytopenia (n=1; 600 mg BID); G3 somnolence (n=1; 600 mg BID)</td>
<td>Olaparib 400 mg BID</td>
</tr>
<tr>
<td>Fong PC, et al (4)</td>
<td>BRCA1/2 mutated ovarian cancer; single-stage expansion of a phase I trial (3)</td>
<td>Dose-Escalation cohort: Olaparib 40 mg PO qd x 2 wks q21d up to 600 mg BID PO qd; Dose-Expansion cohort: Olaparib 200 mg BID PO qd (28-day cycle)</td>
<td>No new DLTs</td>
<td>As per (3)</td>
</tr>
<tr>
<td>Yamamoto N, et al (5)</td>
<td>Advanced solid tumors in Japanese patients</td>
<td>Olaparib 100, 200, or 400 mg BID PO</td>
<td>None</td>
<td>Olaparib 400 mg BID PO</td>
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<tr>
<td><strong>OLAPARIB PLUS CHEMOTHERAPY</strong></td>
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<tr>
<td>Khan OA, et al (6)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 20-200 mg PO days 1-7 plus Dacarbazine 600-800 mg/m² IV d1 (cycle 2, day 2) q21d</td>
<td>Neutropenia, thrombocytopenia</td>
<td>Olaparib 100 mg BID plus Dacarbazine 600 mg/m²</td>
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<tr>
<td>Authors</td>
<td>Tumor Type</td>
<td>Treatment</td>
<td>Toxicities</td>
<td>Notes</td>
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<tr>
<td>Samol J, et al (7)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 50, 100, or 200 mg BID PO plus Topotecan 0.5 or 1 mg/m²/d IV x 3d</td>
<td>Neutropenia, thrombocytopenia</td>
<td>Olaparib 100 mg BID PO plus Topotecan 1.0 mg/m²/d x 3d</td>
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<tr>
<td>Rajan A, et al (8)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 100 mg BID PO d1-4 plus Gemcitabine 500 mg/m² IV d3 and d10 with CDDP 60 mg/m² IV d3</td>
<td>DL1: Thrombocytopenia and febrile neutropenia; GI bleed, syncope, hypoxia</td>
<td>Not determined</td>
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<td>Dent RA, et al (9)</td>
<td>≤1 prior cytotoxic regimen for metastatic TNBC</td>
<td>Olaparib 200 mg BID PO daily plus Paclitaxel 90 mg/m² wkly x 3 wks q 4 wks</td>
<td>G3+ neutropenia (n=6) including 1 case of febrile neutropenia</td>
<td>Not determined</td>
</tr>
<tr>
<td>Del Conte G, et al (10)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 50-400 mg BID PO d1-28 or d1-7 plus PLD 40 mg/m² IV d1</td>
<td>G3 stomatitis and fatal pneumonia/pneumonitis; G4 thrombocytopenia</td>
<td>Continuous/intermittent Olaparib (up to 400 mg BID) plus PLD 40 mg/m² tolerable; MTD using continuous Olaparib not reached</td>
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<td>Balmana J, et al (11)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 50-200 mg BID PO continuously or intermittently (d1-5 or d1-10) plus CDDP 60-75 mg/m²</td>
<td>G3 neutropenia and G3 lipase elevation with continuous olaparib</td>
<td>Olaparib 50 mg BID d1-5 plus CDDP 60 mg/m² (no DLTs)</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Tumor Type</td>
<td>Treatment Details</td>
<td>Toxicity</td>
<td>Dosing Schedule</td>
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<tr>
<td>Bendell J, et al (12)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 50-200 mg BID PO d1-14 q28 days plus Gemcitabine 600-800 mg/m² d1, 8, 15, and 22 (cycle 1), days 1, 8, 15 (cycle 2+)</td>
<td>Increased alanine aminotransferase n=2, neutropenia n=1, febrile neutropenia n=1</td>
<td>Olaparib 100 mg BID d1-14 plus Gemcitabine 600 mg/m²</td>
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<tr>
<td>Chiu et al (13)</td>
<td>Platinum-sensitive and platinum-resistant ovarian cancer</td>
<td>Olaparib 400 mg BID PO d1-7 q21d with escalating dosages of Carboplatin (AUC 3, 4, 5)</td>
<td>G3/4 Neutropenia (n=7, 23%), G3/4 Thrombocytopenia (n=6, 20%)</td>
<td>Olaparib 400 mg BID PO d1-7 plus Carboplatin AUC 4 q21d</td>
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**OLAPARIB PLUS ANTI-ANGIOGENESIS THERAPY**

<table>
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<tr>
<th>Study Authors</th>
<th>Tumor Type</th>
<th>Treatment Details</th>
<th>Toxicity</th>
<th>Dosing Schedule</th>
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<tr>
<td>Dean E, et al (14)</td>
<td>Advanced solid tumors</td>
<td>Olaparib 100, 200 and 400 mg BID PO plus Bevacizumab 10 mg/kg IV q2wk</td>
<td>None</td>
<td>Olaparib 400 mg BID PO plus Bevacizumab 10 mg/kg IV q2wk</td>
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<tr>
<td>Liu JF, et al (15)</td>
<td>Recurrent ovarian (n=20) and metastatic TNBC (n=8)</td>
<td>Olaparib up to 400 mg BID PO and Cediranib 30 mg PO daily</td>
<td>G4 neutropenia (n=1), G4 thrombocytopenia (n=1)</td>
<td>Olaparib 200 mg BID plus Cediranib 30 mg daily</td>
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</table>

Abbreviations: DLT: dose-limiting toxicity; MTD: maximum tolerated dose; CDDP: cisplatin; PLD: pegylated liposomal doxorubicin; BID: two times a day; wk: week; d: day; G: grade; TNBC: triple negative breast cancer.
Table 2. Selected phase II and randomized phase II trials of olaparib alone and in combination.

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<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
<th>PRIMARY ENDPOINT</th>
<th>TOXICOLOGY</th>
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<td><strong>Phase II Olaparib Monotherapy</strong></td>
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<tr>
<td>Tutt A, et al (16)</td>
<td>N=54; recurrent, BRCA 1/2 breast cancer</td>
<td>Cohort 1: Olaparib 400 mg BID PO daily; Cohort 2: Olaparib 100 mg BID PO daily</td>
<td>Cohort 1: ORR 41% Cohort 2: ORR 22%</td>
<td>Cohort 1: G3/4 fatigue (n=4, 15%), G3/4 nausea (n=4, 15%), G3/4 vomiting (n=3, 11%), G3/4 anemia (n=3, 11%)</td>
</tr>
<tr>
<td>Audeh MW, et al (17)</td>
<td>N=57; recurrent, measurable, BRCA 1/2 ovarian cancer</td>
<td>Cohort 1 (n=33): Olaparib 400 mg BID PO daily; Cohort 2 (n=24): Olaparib 100 mg BID PO daily</td>
<td>Cohort 1: ORR 33%, Cohort 2: ORR 13%</td>
<td>Cohort 1: G3/4 nausea (n=2, 6%), G3/4 fatigue (n=1, 3%), G3/4 anemia (n=1, 3%)</td>
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<td>Gelmon KA, et al (18)</td>
<td>N=91; advanced high-grade serous and/or undifferentiated ovarian (N=65) or triple-negative breast cancer (N=26)</td>
<td>Olaparib 400 mg BID PO daily</td>
<td>Ovary: ORR 41% of 17 BRCA 1/2 positive patients and 24% of 46 BRCA negative; Breast: ORR 0%</td>
<td>Ovary: fatigue (70%), nausea (66%), vomiting (39%), decreased appetite (36%).</td>
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<tr>
<td>Kaufman B, et al (19)</td>
<td>N=298; recurrent ovarian, breast, pancreatic, and prostate cancer with BRCA 1/2 mutations</td>
<td>Olaparib 400 mg BID PO daily</td>
<td>Tumor response rate: 31.1% (n=60 of 193: ovarian); 12.9% (breast); 21.7% (pancreatic); 50.0% (prostate)</td>
<td>Most common G3+: anemia (17% entire study population)</td>
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<tr>
<td><strong>Randomized Phase II Olaparib Monotherapy and Maintenance Therapy</strong></td>
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<tr>
<td>Kaye SB, et al (20)</td>
<td>N=97; BRCA1/2 positive ovarian cancer with recurrence &lt; 12 mos of prior platinum therapy</td>
<td>Randomization: Olaparib 200 mg BID PO daily vs Olaparib 400 mg BID PO daily vs PLD 50 mg/m² IV q28 days</td>
<td>PFS and RECIST-assessed ORR n.s. for combined olaparib doses vs PLD</td>
<td>Tolerability as expected based on prior trials</td>
</tr>
<tr>
<td>Ledermann J,</td>
<td>N=265; platinum-</td>
<td>Randomization: Olaparib vs Olaparib</td>
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<tr>
<td>Study</td>
<td>Population</td>
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<td>Results</td>
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<tr>
<td>et al (21)</td>
<td>sensitive, recurrent, high-grade serous ovarian cancer (2 or more prior platinum-based regimens with PR or CR)</td>
<td>Olaparib 400 mg BID PO daily vs. placebo</td>
<td>median PFS 8.4 vs 4.8 mos (HR 0.35; 95% CI, 0.25-0.49; p&lt;0.001); interim analysis for OS n.s.</td>
<td>placebo: nausea (68% vs 35%), fatigue (49% vs 38%), vomiting (32% vs 14%), anemia (17% vs 5%); majority of AEs G1/2</td>
</tr>
<tr>
<td>Ledermann J, et al (22)</td>
<td>N=136 germline BRCA1/2 positive patients from the randomized phase II maintenance study (20); pre-planned retrospective analysis</td>
<td>Olaparib 400 mg BID PO (n=74) vs placebo (n=62)</td>
<td>Olaparib BRCA+ median PFS 11.2 vs 4.3 mos (HR 0.18; 95% CI, 0.10-0.31; p&lt;0.0001); OS n.s.</td>
<td>Olaparib group: G3+ fatigue (7% vs 3%); anemia (5% vs &lt;1%); tolerability similar in women with mutated BRCA and overall population</td>
</tr>
<tr>
<td>Oza AM, et al (23)</td>
<td>N=162; platinum-sensitive, high-grade serous ovarian cancer, up to 3 prior courses of platinum-based chemotherapy, progression-free at least 6 mos</td>
<td>Randomization: Carboplatin AUC 4 mg/mL/min plus Paclitaxel 175 mg/m² IV day 1 with and without Olaparib 200 mg BID PO d1-10 followed by monotherapy 400 mg BID daily</td>
<td>PFS significantly longer in Olaparib + ChemoRx arm: 12.2 mos vs 9.6 mos; HR 0.51; 95% CI, 0.34-0.77; p&lt;0.0012; Among BRCA mutation carriers (n=41: 20 in the Olaparib arm, 21 in the ChemoRx alone arm), HR 0.21; 95% CI, 0.08-0.55; p=0.0015.</td>
<td>Most common G3+ in the Olaparib + ChemoRx arm vs. ChemoRx alone: neutropenia (43% vs 35%); anemia (9% vs 7%).</td>
</tr>
<tr>
<td>Liu JF, et al (24)</td>
<td>N=90; platinum-sensitive, recurrent, high-grade serous or endometrioid ovarian, tubal, or peritoneal cancer and/or germline BRCA 1/2</td>
<td>Randomization: Olaparib 400 mg BID PO twice daily or Olaparib 200 mg BID PO twice daily plus Cediranib 30 mg PO daily</td>
<td>Olaparib plus Cediranib median PFS 17.7 vs 9.0 mos (HR 0.42; 95% CI, 0.23-0.76; p=0.005)</td>
<td>G3/4 more common in combination group: fatigue, diarrhea, hypertension</td>
</tr>
</tbody>
</table>
mutations

Abbreviations: ChemoRx: chemotherapy; PR: partial response; CR: complete response; HR: hazard ratio; CI: confidence interval; G: grade; AE: adverse event; RECIST: Response Evaluation Criteria in Solid Tumors; n.s.: not significant; mos: months.
Figure 1. Mechanism of synthetic lethality between BRCA deficiency and PARP inhibition. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology (ref. 27), copyright 2010.

DNA damage (SSBs)
PARP inhibition impairs base excision repair
DNA replication (DNA DSBs or replication fork collapse)
Normal cell with functional HR pathway
HR-mediated DNA repair
Cell survival
Tumor-selective cell death (synthetic lethality)

HR-deficient tumor cell (BRCA deficient)
Cell death
Impaired HR-mediated DNA repair

Figure 1:
Clinical Cancer Research

Development of Olaparib for BRCA-Deficient Recurrent Epithelial Ovarian Cancer

Krishnansu S. Tewari, Ramez N. Eskander and Bradley J. Monk

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